

INSULIN RECEPTOR ACTIVATORS FOR THE TREATMENT OF
METABOLIC DISORDERS INDUCED BY TREATMENT WITH HIV
PROTEASE INHIBITORS

5 CROSS-REFERENCE TO RELATED APPLICATION

This application claims the priority under 35 USC 119(e) of US Provisional
Application No. 60/239,636, filed October 11, 2000, which is incorporated herein by
reference.

10 BACKGROUND OF THE INVENTION

(a) Field of the Invention

The present invention relates to methods, chemical compounds, and compositions for
15 the treatment of metabolic disorders induced by treatment with HIV protease inhibitors.

(b) Description of Related Art

Treatments for HIV infection have proven very effective in controlling the ravages of
the terminal stage of the infection, AIDS. The HIV protease inhibitors are an extremely
20 important component in the drug regimens used to suppress viral load and the resulting AIDS
symptoms. Unfortunately, these drugs which are required to maintain health in HIV-infected
individuals also carry a significant side-effect burden. One of the recently recognized severe
side-effects is HIV protease inhibitor-induced insulin resistance leading to hyperglycemia that
can progress to diabetes and ultimately life threatening ketoacidosis. (Carr, A., Samaras, K.,
25 Chrisholm, D.J., and Cooper, D.A. (1998) *Lancet* 351 1881-1883; Carr, A., Samaras, K.,
Burton, S., Freund, I., Chisholm, D.J., Cooper D.A. (1998) *AIDS* 12, F51-F58).

In addition to insulin resistance, other related disturbances in metabolism, such as
lipodystrophy and hypertriglyceridemia, are also observed in HIV protease inhibitor treated
patients (Roth, V.R., Kravcik, S., Angel, J.B. (1998) *Clin Infect Dis* 27,65-67; Safrin, S., and
30 Grunfeld, C., (1999) *AIDS* 13, 2493-2505; Carr, A., Samaras, K., Thorisdottir, A., Kaufmann,
G.R., Chrisholm, D.J., and Cooper, D.A. (1999) *Lancet* 353, 2093-2099; Behrens, G.,